

LISTING OF THE CLAIMS

This listing of claims will replace all prior versions, and listings, of claims in the application:

1. (Currently Amended) ~~An oral pharmaceutical composition for delivery of a physiologically active peptide agent that is not naturally amidated at its C-terminus, said composition comprising an therapeutically effective amount of said active peptide agent that wherein said active peptide has an amide group added at its C-terminus, and is not found in nature with an amide group at its C-terminus, said composition further comprising an absorption enhancer effective to promote bioavailability of said active peptide agent, or a pharmaceutically acceptable pH-lowering agent that is present in said pharmaceutical composition in a quantity which, if said composition were added to ten milliliters of 0.1M aqueous sodium bicarbonate solution, would be sufficient to lower the pH of said solution to no higher than 5.5.~~

2. (Currently amended) The pharmaceutical composition of claim 1 further comprising at least one pharmaceutically acceptable pH-lowering agent ~~and/or protease inhibitor.~~

3. (Original) The pharmaceutical composition of claim 2 further comprising an acid resistant protective vehicle effective to transport said pharmaceutical composition through the stomach of a patient while preventing contact between said active peptide agent and stomach proteases.

Claim 4 (Canceled).

5. (Currently Amended) The pharmaceutical composition of claim 1, wherein said active peptide agent is prepared as by converting a glycine-extended precursor and subsequently converted to a C-terminal amide group ~~said active peptide agent.~~

6. (Currently amended) The pharmaceutical composition of claim 1, wherein said active peptide agent comprises an amino acid that contains an amidated side chain.

7. (Canceled)

8. (Original) The pharmaceutical composition of claim 2, wherein said pH-lowering agent is present in a quantity which, if said composition were added to ten milliliters of 0.1M aqueous sodium bicarbonate solution, would be sufficient to lower the pH of said solution to no higher than 3.5.

9. (Canceled)

10. (Canceled)

11. (Original) The pharmaceutical composition of claim 1, wherein said active peptide agent is linked to a membrane translocator which is capable of being at least partially cleaved in vivo by an enzyme.

12. (Original) The pharmaceutical composition of claim 3, wherein said protective vehicle is present at a weight which is no more than 30% of the weight of the remainder of said pharmaceutical composition.

13. (Original) The pharmaceutical composition of claim 3, wherein said protective vehicle is present at a weight which is no more than 20% of the weight of the remainder of said pharmaceutical composition.

14. (Original) The pharmaceutical composition of claim 3, wherein said protective vehicle is present at a weight which is between 10% and 20% of the weight of the remainder of said pharmaceutical composition.

15. (Original) The pharmaceutical composition of claim 3, wherein said protective vehicle is sufficient to prevent breakdown of said pharmaceutical composition in 0.1N HCl for at least two hours, yet permits complete release of all contents of said pharmaceutical composition

within 45 minutes after pH is increased to 6.3 in a dissolution bath in which said composition is rotating at 100 revolutions per minute.

16. (Canceled).

17. (Currently amended) The pharmaceutical composition of claim 1, ~~wherein said comprising an absorption enhancer, wherein the absorption enhancer~~ is a surface active agent.

18. (Original) The pharmaceutical composition of claim 17, wherein said surface active agent is absorbable or biodegradable.

19. (Original) The pharmaceutical composition of claim 17, wherein said surface active agent is selected from the group consisting of acylcarnitines, phospholipids and bile acids.

20. (Currently amended) The pharmaceutical composition of claim 19, wherein said ~~enhancer surface active agent is an acyl carnitine~~ acylcarnitine.

21. (Original) The pharmaceutical composition of claim 20, further including a sucrose ester.

22. (Currently amended) The pharmaceutical composition of claim 1, ~~wherein said comprising an absorption enhancer, wherein the absorption enhancer~~ is a surface active agent selected from the group consisting of (i) an anionic agent that is a cholesterol derivative, (ii) a mixture of a negative charge neutralizer and an anionic surface active agent, (iii) non-ionic surface active agents, and (iv) cationic surface active agents.

23. (Currently amended) The pharmaceutical composition of claim 1, ~~wherein said comprising an absorption enhancer~~ is selected from the group consisting of a cationic surfactant and an anionic surfactant that is a cholesterol derivative.

24. (Previously Presented) The pharmaceutical composition of claim 1, wherein said pharmaceutical composition includes at least two absorption enhancers, one of which is a cationic surface active agent, and another of which is an anionic surface active agent that is a cholesterol derivative.

25. (Original) The pharmaceutical composition of claim 24, wherein said anionic surface active agent is an acid-soluble bile acid.

26. (Currently amended) The pharmaceutical composition of claim 1, further comprising an amount of a second peptide that is not a physiologically active peptide effective to enhance bioavailability of said peptide active agent.

27. (Original) The pharmaceutical composition of claim 3, further comprising a water soluble barrier that separates said pH-lowering agent from said protective vehicle.

28. (Original) The pharmaceutical composition of claim 2, wherein said composition includes at least one pH-lowering agent that has a pKa no higher than 4.2.

29. (Original) The pharmaceutical composition of claim 2, wherein at least one pH-lowering agent has a solubility in water of at least 30 grams per 100 milliliters of water at room temperature.

30. (Original) The pharmaceutical composition of claim 3, wherein all ingredients other than said protective vehicle are uniformly dispersed.

31. (Original) The pharmaceutical composition of claim 30, wherein said pharmaceutical composition comprises granules containing a pharmaceutical binder and, uniformly dispersed in said binder, said pH-lowering agent, said absorption enhancer and said peptide active agent.

32. (Currently amended) The pharmaceutical composition of claim 1, comprising a pharmaceutically acceptable pH-lowering agent and an absorption enhancer wherein said composition is a solid dosage form wherein a weight ratio of said pH-lowering agent to said absorption enhancer is between 3:1 and 20:1.

33. (Currentlt amended) The pharmaceutical composition of claim 1, comprising a pharmaceutically acceptable pH-lowering agent and an absorption enhancer wherein said composition is a solid dosage form wherein the weight ratio of said pH-lowering agent to said absorption enhancer is between 5:1 and 10:1.

34. (Original) The pharmaceutical composition of claim 2, wherein said pH-lowering agent is selected from the group consisting of citric acid, tartaric acid and an acid salt of an amino acid.

35. (Original) The pharmaceutical composition of claim 2, wherein said pH-lowering agent is present in an amount not less than 300 milligrams.

36. (Original) The pharmaceutical composition of claim 35, wherein said pH-lowering agent is present in an amount which is not less than 400 milligrams.

37. (Currently amended) The pharmaceutical composition of claim 1, wherein said active peptide agent is human glucagon-like peptide 1, human glucagon-like peptide 2 or analog thereof.

Claim 38 (Canceled)

39. (Currently amended) The pharmaceutical composition of claim 1, wherein said active peptide agent is insulin.

40. (Currentlt amended) The pharmaceutical composition of claim 1, wherein said active peptide agent is human parathyroid hormone or analog thereof.

41. (Currently amended) The pharmaceutical composition of claim 1, wherein said active peptide agent is a human parathyroid hormone analog PTH 1-31NH₂ having the first 31 amino acids of human parathyroid hormone wherein the 31st amino acid has the amide group.

42. (Currently Amended) ~~An oral~~ The pharmaceutical composition of claim 1 adapted to provide enhanced bioavailability of orally delivered PTH 1-34NH₂, said composition comprising a therapeutically effective amount of ~~wherein said active peptide agent is a human parathyroid hormone analog PTH 1-34NH₂, wherein said PTH 1-34NH₂ is amidated at its C-terminus where it is not naturally amidated, and an absorption enhancer effective to promote bioavailability of said PTH 1-34NH₂ having the first 34 amino acids of human parathyroid hormone wherein the 34th amino acid is amidated at its C-terminus.~~

43. (Original) The pharmaceutical composition of claim 3, wherein said protective vehicle is a viscous protective syrup.

44. (Currently amended) The pharmaceutical composition of claim 34 ~~2~~, wherein a water soluble barrier separates said pH-lowering agent from said protective vehicle.

45. (Currently Amended) ~~A method for enhancing the bioavailability of an orally delivered~~ modifying a physiologically active peptide to increase its oral bioavailability, while substantially maintaining its physiological activity, said method agent comprising:

(A) amidating a physiologically active peptide agent that is not naturally amidated at its C-terminus at said C-terminus; and

(B) orally administering said amidated peptide ~~agent~~ in combination with (i) at least one absorption enhancer effective to promote bioavailability of said ~~active~~ amidated peptide ~~agent~~, or (ii) a pH-lowering agent that is present in said pharmaceutical composition in a quantity which, if said composition were added to ten milliliters of 0.1M aqueous sodium bicarbonate solution, would be sufficient to lower the pH of said solution to no higher than 5.5.

46. (Currently amended) The method of claim 45 comprising an absorption enhancer, wherein said amidated peptide active agent and said absorption enhancer are selectively released together with at least one pH-lowering agent and/or protease inhibitor into a patient's intestine following passage of said peptide active agent, absorption enhancer, pH-lowering agent and/or protease inhibitor through said patient's mouth and stomach under protection of an acid resistant protective vehicle which substantially prevents contact between stomach proteases and said peptide agent.

Claim 47 (Canceled).

48. (Currently Amended) The method of claim 45 47, wherein said active amidated peptide agent is prepared as by converting a glycine-extended precursor and subsequently converted to a C-terminal-amide group said amidated peptide.

49. (Currently amended) The method of claim 45, wherein said amidated active peptide further includes ~~is amidated at an amino acid~~ amidated side chain.

50. (Currently amended) The method of claim 45 46, wherein said pH-lowering agent and said absorption enhancer are both present ~~is present in said pharmaceutical composition in a quantity which, if said composition were added to ten milliliters of 0.1M aqueous sodium bicarbonate solution, would be sufficient to lower the pH of said solution to no higher than 5.5.~~

51. (Currently amended) The method of claim 46 45 comprising a pH-lowering agent , wherein said pH-lowering agent is present in a quantity which, if said composition were added to ten milliliters of 0.1M aqueous sodium bicarbonate solution, would be sufficient to lower the pH of said solution to no higher than 3.5.

52. (Original) The method of claim 46, wherein said protease inhibitor is a stomach and/or intestine protease inhibitor.

53. (Original) The method of claim 46, wherein said protease inhibitor inhibits an enzyme selected from the group consisting of pepsin, trypsin, chymotrypsin, elastase, kallikrein and carboxypeptidase.

Claim 54 (Canceled).

55. (Currently amended) The method of claim 45, wherein said physiologically active peptide agent is human glucagon-like peptide 1, human glucagon-like peptide 2, or an analog thereof.

Claim 56 (Canceled).

57. (Currently amended) The method of claim 45, wherein said physiologically active peptide agent is insulin.

58. (Currently amended) The method of claim 45, wherein said physiologically active peptide agent is human parathyroid hormone or an analog thereof.

59. (Currently amended) The method of claim ~~58~~ 45, wherein said amidated peptide agent is human parathyroid hormone analog PTH 1-31-NH₂.

60. (Currently Amended) ~~A The method for enhancing the bioavailability of orally delivered of claim 45 wherein said amidated peptide is~~ human parathyroid hormone analog PTH1-34-NH₂ comprising:

—— (A) —— amidating said PTH 1-34-NH₂ at its C-terminus where it is not naturally amidated; and

—— (B) —— orally administering said PTH 1-34-NH₂ in combination with at least one absorption enhancer effective to promote bioavailability of said PTH 1-34-NH₂.

Claims 61-62 (Canceled).

63. (Currently amended) The method of claim 45, wherein said ~~enhancement of~~
increase in oral bioavailability is the result of enhanced intestinal absorption of the amidated
peptide.

Claims 64-65 (Canceled).